Problem: Gender Dysphoria and Disorders of Sexual Differentiation

I.1

I.1.1 Gender Dysphoria

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Key Messages

- Transsexualism is a condition in which a person with apparently normal somatic sexual differentiation is convinced that he or she is actually a member of the opposite sex.
- The aetiology of transsexualism remains uncertain.
- Clinical examination, like measurement of sex hormone levels and karyotyping, is unlikely to yield anything more than confirmation of biological sex.
- Hormonal reassignment aims at reducing the hormonally induced secondary sex characteristics of the original sex and at inducing the secondary sex characteristics of the new sex.
- The quality of surgical construction of the genitalia is crucial for all transsexuals.
- Transsexual individuals require long-term assistance to optimize cross-sex hormone treatment.
- Few transsexuals regret undergoing treatment.

I.1.1.1 Definition

Transsexualism is a condition in which a person with apparently normal somatic sexual differentiation is convinced that he or she is actually a member of the opposite sex. It is associated with an irresistible urge to be hormonally and surgically adapted to that sex.

Gender dysphoria is a self-diagnosis with no supporting tests other than persistence of dysphoria for at least 2 years, alleviated by cross-gender identification psychosocially, anatomically, and hormonally. Self-diagnosis is confirmed by psychological assessment, which includes a trial period, "the real life test". This period when hormonal treatment starts and subjects are required to live socially the life of the desired sex is necessary before irreversible surgical reassignment is considered.

Gender identity disorder has three criteria according to DSM-IV:

1. The desire to live and be accepted as a member of the opposite sex, usually accompanied by the wish to make his or her body as congruent as possible with the preferred sex through surgery and hormone treatment.
2. The transsexual identity has been present persistently.
3. The disorder is not a symptom of another mental disorder or a chromosomal abnormality.

I.1.1.2 Aetiology and Pathogenesis

The aetiology of transsexualism remains uncertain (Gooren 1990; Zhou et al. 1995). The most recent prevalence information from the Netherlands is 1 in 11,900 males and 1 in 30,400 females (van Kesteren et al. 1996).

I.1.1.3 Clinical Findings

Before any physical intervention is considered, extensive exploration of psychological, family and social issues should be undertaken. A clear explanation of the irreversible effects of hormone therapy on body habitus is necessary. The physician should counsel the patient about realistic expectations from treatment and discuss the treatment options, both hormonal and surgical.

Biologic males, especially those who have not already reproduced, should be informed about sperm preservation options, and they can consider banking sperm prior to hormonal therapy (De Sutter 2001). Biologic females do not presently have readily available options for gamete preservation, other than cryopreservation of fertilized embryos.

Physical assessment, to be approached with care, should include a full examination of secondary sexual

characteristics. Clinical examination, like measurement of sex hormone levels and karyotyping, baseline cholesterol, urea and electrolytes, glucose and liver function tests, is unlikely to yield anything more than confirmation of biological sex, aside from potentially disclosing evidence of self-treatment (Levy et al. 2003). Basic medical monitoring should include serial physical examinations relevant to treatment effects and side effects, vital sign measurements before and during treatment, weight measurements, and laboratory assessment.

For those receiving oestrogens, the minimum laboratory assessment should consist of a pretreatment (free) testosterone level, fasting glucose, liver function tests, and complete blood count with reassessment at 6 and 12 months and annually thereafter. A pretreatment prolactin level should be obtained and repeated on a yearly basis. Biologic males undergoing oestrogen treatment should be monitored for breast cancer and encouraged to engage in routine self-examination. As they age, they should be monitored for prostatic cancer (van Haarst et al. 1998).

For those receiving androgens, the minimum laboratory assessment should consist of pretreatment liver function tests and haematocrit/complete blood count with reassessment at 6 months, 12 months, and yearly thereafter.

I.1.1.4 Treatment

I.1.1.4.1 Standards of Care

The international organization involved with professional help to transsexuals, the Harry Benjamin International Gender Dysphoria Association, has drafted standards of care. The major purpose of the standards of care is to articulate this organization's professional consensus about the psychological, medical, and surgical management of gender identity disorders. These standards provide guidance to professionals practising in this area.

I.1.1.4.2 Physical Interventions

A staged process is recommended to keep options open through the reversible stage. Moving from one state to another should not occur until there has been adequate time for the person and his or her family to assimilate fully the effects of earlier interventions. Arguments include psychosocial reasons and, furthermore, a more gradual adaptation of the body to a changing hormonal milieu. It is our belief that a slow transition phase of usually 2 years, rather than a quick one, may be more advisable (T'Sjoen et al. 2004).

Reversible Interventions

These interventions involve the use of luteinizing hormone releasing hormone (LHRH) agonists, cyproterone acetate or medroxyprogesterone to suppress oestrogen or testosterone production in order to reduce the hormonally induced secondary sex characteristics of the original sex as much as possible.

Irreversible Interventions

These include hormonal interventions that masculinize or feminize the body, such as administration of testosterone to biologic females and oestrogen to biologic males, and the surgical procedures.

I.1.1.4.3 Hormonal Sex Reassignment

Hormonal treatment, when medically tolerated, should precede any genital surgical interventions. Satisfaction with the hormone's effects consolidates the person's identity as a member of the preferred sex and gender and further adds to the conviction to proceed. Dissatisfaction with hormonal effects may signal ambivalence about proceeding to surgical interventions. Some individuals who receive hormonal treatment will not desire genital or other surgical interventions (Table I.1.1).

Table I.1.1. Recommended hormonal treatment regimens and follow-up for transsexuals

	Male to female	Female to male
Treatment		
Psychological assessment		
Hormonal treatment		
Reversible phase	Antiandrogen	Progestin
Irreversible phase	Antiandrogen + oestrogens	Testosterone
Follow-up		
Initial visit	Karyotype Measurement of sex hormone levels Weight Lipid profile Liver function tests	Karyotype Measurement of sex hormone levels Weight Lipid profile Liver function tests
Every 4 months preoperative	Testosterone levels Weight Lipid profile Liver function tests Serum prolactin	Testosterone levels Weight Lipid profile Liver function tests Complete blood count
Every 6 months to 1 year postoperative	Same parameters, include Dexa scan. Over 50 years: PSA Encourage breast exams	Same parameters, include Dexa scan.

Hormonal reassignment has two aims (Asscheman and Gooren 1992):

1. To reduce the hormonally induced secondary sex characteristics of the original sex as much as possible, but complete elimination is rare. For example, in male-to-female transsexuals, the previous effects of androgens on the skeleton, such as the greater height of men than women, the size and shape of hands, feet, jaws and pelvis, cannot be reversed. Conversely, the relatively lower height and the broader hip configuration of female-to-male transsexuals compared to men will not change with androgen treatment.
2. To induce the secondary sex characteristics of the new sex.

Biologic Males

- Antiandrogens
  Several agents are available to inhibit androgen secretion or action. In Europe, the most widely used drug is cyproterone acetate (usually 50 mg daily), a progestational compound with antiandrogenic properties. If it is not available, medroxyprogesterone acetate, 5 – 10 mg/day, is an alternative, although less effective. Nonsteroidal antiandrogens, such as flutamide and nilutamide, are also used, but they increase gonadotrophin secretion, causing increased secretion of testosterone and oestradiol; the latter is a desirable effect in this context. Spironolactone (100 mg twice daily), a diuretic with antiandrogenic properties, has similar effects. Long-acting gonadotrophin-releasing hormone (GnRH) agonists, used as monthly injections, also inhibit gonadotrophin secretion. Finasteride (1 – 5 mg/day), a 5α-reductase inhibitor, might also be considered.
- Oestrogens
  Oestrogen treatment can realistically be expected to result in breast growth, some redistribution of body fat to approximate a female body habitus, decreased upper body strength, softening of skin, decrease in body hair, slowing or stopping the loss of scalp hair, decreased fertility and testicular size and less firm erections. Breast formation starts almost immediately after initiation of oestrogen administration. Androgens have an inhibitory effect on breast formation and, therefore, oestrogens will be most effective in a milieu devoid of androgen action. After 2 years of oestrogen administration, no further development can be expected. It is estimated to be quantitatively satisfactory in 40 % to 50 % of subjects. The attained size is often disproportional to the male dimension of the chest and height of the subject, so the subject may desire surgical breast augmentation. Adult male beard growth is very resistant to inhibition by combined hormonal intervention, and in Caucasian subjects additional measures to eliminate facial hair are necessary. Sexual hair growth on other parts of the body responds more favourably (Giltay and Gooren 2000). Antiandrogens and oestrogens have no effect on the properties of the voice, so male-to-female transsexuals may wish to consult a specialized phoniatric centre for speech therapy (Van Borsel et al. 2001).

There is a wide range of oestrogens from which to choose. The use of transdermal oestrogen patches should be considered for males over 40 years of age or those with clotting abnormalities or a history of venous thrombosis (Moore et al. 2003). Attempts to mimic the menstrual cycle by prescribing interrupted oestrogen therapy or substituting progesterone for oestrogen during part of the month are not necessary to achieve feminization.

Biologic Females

The goal of treatment in female-to-male transsexuals is to induce virilization, including a male pattern of sexual hair and male physical contours, and to stop menses.

- Progestins, e.g. medroxyprogesterone acetate 5 – 10 mg/day, to stop menstrual bleeding
- Testosterone

Androgen administration induces the following permanent changes: a deepening of the voice after 6 – 10 weeks, clitoral enlargement, mild breast atrophy, increased facial and body hair and male pattern baldness. Other changes include increased upper body strength, weight gain, increased social and sexual interest and arousability, and decreased hip fat. Viable options of androgen treatment include oral, injectable, and transdermal delivery systems. Treatment principles are equal to those for treatment of the hypogonadal male patient.

Potential Negative Medical Side Effects

In a review of 816 male-to-female transsexuals and 293 female-to-male transsexuals (total exposure 10,152 patient years), mortality was no higher than in a comparison group (Van Kesteren et al. 1997). However, cross-sex hormone administration may be associated with the side effects listed below.

Increased propensity in biologic males treated with oestrogens and antiandrogens to blood clotting (venous thrombosis with a risk of fatal pulmonary embolism), development of benign pituitary prolactinomas, infertility, weight gain, emotional lability, liver disease, somnolence, hypertension, and diabetes mellitus.

Side effects in biologic females treated with testosterone may include infertility, acne, emotional lability, increases in sexual desire, and shift of lipid profiles to male patterns which increase the risk of cardiovascular disease. Ovaries of female-to-male transsexuals taking androgens show similarities with polycystic ovaries, which are also more likely to develop malignancies. Therefore, it seems reasonable to remove the ovaries of androgen-treated female-to-male transsexuals after a successful transition to the male role.

Contraindications against the use of high doses of either sex steroid are cardiovascular disease, cerebrovascular disease, thromboembolic disease, marked obesity, poorly controlled diabetes mellitus, and active liver disease. Risk-benefit ratios should be considered collaboratively by the patient and prescribing physician (Michel et al. 2001).

Post-transition Follow-up

Postoperative patients may also sometimes exclude themselves from follow-up with the physician prescribing hormones, not recognizing that these physicians are best able to prevent, diagnose and treat possible long-term medical conditions that are unique to hormonally and surgically treated patients. Postoperative patients should undergo regular medical screening according to recommended guidelines for their age.

Close monitoring and yearly reevaluation of treatment are also important to minimize the adverse effects while maximizing the benefits. After reassignment surgery, including orchiectomy, hormone therapy must be continued. Continuous oestrogen therapy is required to avoid symptoms of hormone deprivation and, most importantly, to prevent osteoporosis. After bilateral oophorectomy, androgen therapy must be continued to maintain virilization and prevent osteoporosis (Van Kesteren 1998).

I.1.1.4.4 Surgical Sex Reassignment

The procedures differ depending upon the direction of the sex change (Monstrey et al. 2001).

Male-to-female: A neovagina is surgically constructed, usually using the penile skin for vaginal lining and scrotal skin for the labia. If breast development is judged to be insufficient, the breasts may be surgically augmented. Because immobilization is also a risk factor for venous thromboembolic events, oral oestrogen administration should be discontinued 3–4 weeks before elective surgical interventions. Once subjects are fully mobilized again, oral oestrogen therapy may be resumed.

Female-to-male: The breasts, uterus and ovaries are surgically removed. In rare cases, the hypertrophied clitoris may serve as a phallus. In other cases a so-called metaidoioplasty may be performed. Free flaps removed from arms or legs can be used to construct a neophallus. These surgical interventions allow the person to urinate standing. From the labia majora, a scrotum can be constructed in which testicular prostheses can be implanted. An erection prosthesis may be optional. The quality of surgical construction of the genitalia is crucial for all transsexuals to permit them to adopt credibly the role of a member of the new sex.

I.1.1.5 Prognosis

Although more evidence would be welcome, adequately treated gender dysphoria is likely to be safer than the untreated condition, which is associated with an enhanced risk of depression and suicide. Reassuringly, few transsexuals regret undergoing treatment (Pfäfflin 1992).

A team of professionals with an interest in the gender identity disorders can provide optimal care. Doubts about the authenticity of gender dysphoria as a diagnosis, lack of approbation from peers and perhaps personal phobias may lead some members of the medical profession to withhold treatment. Transsexual individuals require long-term assistance to optimize cross-sex hormone treatment and should not be subject to discrimination when they seek health care.

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I.1.2 Disorders of Sexual Differentiation

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Key Messages

- Individuals who have a genital appearance that does not permit gender declaration are said to have ambiguous genitalia.
- Intersex is not confined to infants at birth.
- The commonest cause of newborn intersex is congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency.
- The commonest cause of the under-masculinized male is the group of androgen insensitivity syndromes.
- Gonadal histology is needed to confirm a diagnosis of hermaphroditism.
- The urgent medical issue is the possibility of adrenal crisis (a life-threatening emergency) in infants with the salt-wasting form of CAH.
- The birth of an infant with ambiguous genitalia is a psychosocial emergency for the family.

I.1.2.1 Definition

Individuals who have a genital appearance that does not permit gender declaration are said to have ambiguous genitalia. This includes infants with perineal hypospadias with bifid scrotum, bilateral cryptorchidism, clitoromegaly, posterior labial fusion, phenotypic female appearance with palpable gonad, and infants with discordant genitalia and sex chromosomes. XY infants with palpable gonads and simple hypospadias or microphallus, although under-virilized, do not have truly ambiguous genitalia and are discussed separately in other chapters. Intersex is not confined to infants at birth. Nonisosexual development can occur at puberty. Examples include 17β-hydroxydehydrogenase deficiency and 5α-reductase enzyme deficiencies, late-onset congenital adrenal hyperplasia (CAH) and partial androgen insensitivity syndrome (PAIS).

I.1.2.2 Aetiology and Pathogenesis

The investigation and management of disorders of sexual differentiation is dependent on an understanding of the embryology, genetics and hormonal control of normal foetal sex development (see Sects. 2.1.2 and 2.2.2 in Chap. 2). Knowledge of postnatal psychosexual development and an appreciation of the sociocultural influences on gender is very important. History taking should include the following information: family tree with females who are childless or have amenorrhea, history of consanguinity, prenatal exposure to androgens (e.g. danazol, testosterone) or teratogens or endocrine disruptors (phenytoin, aminoglutethimide) (Dessens et al. 2001), and a history of unexplained infant deaths (CAH).

I.1.2.3 Classification of Intersex

We have traditionally used prefixes to the word, hermaphroditism, to classify intersex: female pseudohermaphroditism (e.g. congenital adrenal hyperplasia) and male pseudohermaphroditism (androgen insensitivity syndrome) (Table I.1.2).

This terminology is confusing for medical staff and patients. A simpler format, as has been suggested by ex-

Table I.1.2. Phenotypic characteristics possibly reflecting disordered sexual differentiation

Female phenotype	Ambiguous phenotype	Male phenotype
Isolated clitoromegaly	Ambiguous genitalia	Male with nonpalpable testes
Isolated labial fusion		Micropenis, bifid scrotum
Palpable gonads, inguinal herniae	Syndromal genital anomalies	Severe hypospadias ± undescended testes